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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

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Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv)) for US only

Published:

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **BRANCHED WATER-SOLUBLE POLYMERS AND THEIR CONJUGATES**

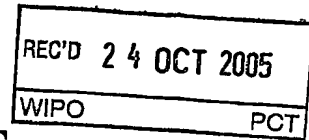
(57) Abstract: The present invention provides branched water-soluble polymers that allow two or more water-soluble polymers to be conjugated to another species. The branched polymers provide access to therapeutic agents that are conjugated at a single site to two or more water-soluble polymers. The branched polymers are based upon branch points that are simple branched alkyl structures, reactive side-chain amino acids and small peptides of reactive side-chain amino acids, and saccharides. Also provided is a method for preparing mono-disperse poly(ethylene glycol) of a well-defined and determinable molecular weight, and a method for the rational end-functionalization of poly(ethylene glycol). Conjugates of the branched water-soluble polymers with diverse species, e.g., peptides, lipids, glycolipids and small molecules are also provided.



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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY



PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

| | | | |
|--|--|--|--|
| To: JEFFRY S. MANN TWO EMBARCADERO CENTER, 8 TH FLOOR SAN FRANCISCO, CALIFORNIA 94111 | | | Date of mailing (day/month/year) 20 OCT 2005 |
| Applicant's or agent's file reference 19957-184-2P | | | FOR FURTHER ACTION See paragraph 2 below |
| International application No. PCT/US04/07931 | International filing date (day/month/year) 15 March 2004 (15.03.2004) | Priority date (day/month/year) 14 March 2003 (14.03.2003) | |
| International Patent Classification (IPC) or both national classification and IPC IPC(7): A01N 43/04; A61K 31/70 and US Cl.: 514/2, 7, 42, 43, 49, 50, 51, 52 | | | |
| Applicant NEOSE TECHNOLOGIES, INC. | | | |

1. This opinion contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|--|
| <input checked="" type="checkbox"/> | Box No. I | Basis of the opinion |
| <input type="checkbox"/> | Box No. II | Priority |
| <input type="checkbox"/> | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> | Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> | Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> | Box No. VI | Certain documents cited |
| <input type="checkbox"/> | Box No. VII | Certain defects in the international application |
| <input type="checkbox"/> | Box No. VIII | Certain observations on the international application |

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| | | |
|--|--|--|
| Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230 | Date of completion of this opinion 02 September 2005 (02.09.2005) | Authorized officer Patrick T. Lewis <i>Janice Foul</i> Telephone No. 571-272-1600 <i>for</i> |
|--|--|--|

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US04/07931

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

- ☐ a sequence listing
☐ table(s) related to the sequence listing

b. format of material

- ☐ on paper
☐ in electronic form

c. time of filing/furnishing

- ☐ contained in the international application as filed.
☐ filed together with the international application in electronic form.
☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/07931

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|--------------------|-----|
| Novelty (N) | Claims <u>1-38</u> | YES |
| | Claims <u>NONE</u> | NO |
| Inventive step (IS) | Claims <u>1-38</u> | YES |
| | Claims <u>NONE</u> | NO |
| Industrial applicability (IA) | Claims <u>1-38</u> | YES |
| | Claims <u>NONE</u> | NO |

2. Citations and explanations:

Claims 1-38 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the instantly claimed peptides, amino acids, or water-soluble polymers.

Claims 1-38 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/07931

| A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : A01N 43/04; A61K 31/70 US CL : 514/2, 7, 42, 43, 49, 50, 51, 52 According to International Patent Classification (IPC) or to both national classification and IPC | | |
|--|---|--|
| B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/2, 7, 42, 43, 49, 50, 51, 52 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) WEST, CAPLUS, REGISTRY | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT | | |
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| A | ABELION et al. "3'-O-(4-Benzoyl)benzoylcytidine 5'-triphosphate", The Journal of Biological Chemistry, 1986, Vol. 261, No. 24, pages 11374-11377. | 1-38 |
| A | US 4,565,653 (IVES et al.) 21 January 1986 (21.01.1986) see entire document. | 1-38 |
| <input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex. | | |
| * Special categories of cited documents: | | |
| "A" | document defining the general state of the art which is not considered to be of particular relevance | "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "B" | earlier application or patent published on or after the international filing date | "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "L" | document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "O" | document referring to an oral disclosure, use, exhibition or other means | "&" document member of the same patent family |
| "P" | document published prior to the international filing date but later than the priority date claimed | |
| Date of the actual completion of the international search 02 September 2005 (02.09.2005) | | Date of mailing of the international search report 20 OCT 2005 |
| Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230 | | Authorized officer Patrick T. Lewis <i>Janice Ford</i> Telephone No. 571-272-1600 |